

## Penicillin Allergies

### Penicillin Allergies – Guide for Clinicians

#### Prevalence of Penicillin Allergy:

Approximately 10% of the patient population will report an allergic reaction to a penicillin class antibiotic. Of those who report a history of penicillin allergy, up to 90% are able to tolerate penicillins when challenged (1-3).

The reasons for the discrepancy between reported and actual penicillin allergy may be due to:

- Waning of penicillin specific IgE antibodies over time. It has been reported that up to 80% of patients may lose their IgE-mediated sensitivity to penicillins after 10 years of the initial reaction.
- A cutaneous reaction that was initially thought to be an allergy, but was actually a result of the underlying viral or bacterial infection, or an interaction between the infectious agent and the antibiotic given at the time.
- A drug side effect mislabeled as an allergic reaction.

The rate of penicillin-induced anaphylaxis is rare and is reported to be less than 1% in the literature (2, 4).

#### Coombs and Gell Hypersensitivity Classification (5, 6):

| Classification                                  | Mediator                   | Onset                        | Onset (previously sensitized) | Possible Clinical Reactions   | Use skin testing? |
|---|----------------------------|------------------------------|-------------------------------|---|-------------------|
| <b>I – Immediate-type hypersensitivity</b>      | IgE antibodies             | 0 to 1 hr (up to 72 hrs)     | 0 to 1 hr                     | Anaphylaxis, urticaria, angioedema, wheezing, hypotension                               | Yes               |
| <b>II – Antibody-antigen binding</b>            | IgG or IgM antibodies      | > 72 hrs (up to 14 days)     | 24 to 36 hr                   | Hemolytic anemia, neutropenia, thrombocytopenia   | No                |
| <b>III – Soluble antigen-antibody complexes</b> | Antigen-antibody complexes | > 72 hours (up to 14 days)   | 24 to 36 hr                   | Serum sickness, vasculitis, drug fever, glomerulonephritis                              | No                |
| <b>IV – Delayed-type hypersensitivity</b>       | T-cells                    | > 72 hours (up to 3-4 weeks) | 48 to 96 hr                   | Contact dermatitis, morbilliform eruptions, Steven-Johnson / toxic epidermal necrolysis | No                |

#### Penicillin-Cephalosporin Cross-Sensitivity:

The rate of penicillin-cephalosporin cross-sensitivity is overestimated in the literature and is likely dependent on the presence of a shared side chain with the penicillin rather than the core beta-lactam ring of the drug's molecular structure (2,7). A higher risk of allergic reaction is expected with cephalosporins that share a similar side chain as a beta-lactam to which a patient is allergic (see cross-sensitivity chart below).

**\*\*Please refer to the “Algorithm for Management of Penicillin Allergy” to help determine if a patient can safely be given a penicillin or cephalosporin and if performing penicillin skin testing is appropriate\*\***

## Penicillin-Cephalosporin-Carbapenem Cross-Sensitivity Chart (8, 9):

|  |              | Amoxicillin   | Ampicillin | Cloxacillin | Penicillin | Piperacillin | Cefadroxil | Cefazolin | Cephalexin | Cephalothin | Cefaclor | Cefprozil | Cefotetan | Cefoxitin | Cefuroxime | Cefixime | Cefotaxime | Ceftazidime | Ceftriaxone | Cefepime | Ertapenem | Imipenem | Meropenem |   |
|--|--------------|---|------------|-------------|------------|--------------|------------|-----------|------------|-------------|----------|-----------|-----------|-----------|------------|----------|------------|-------------|-------------|----------|-----------|----------|-----------|---|
| Penicillins                              | Amoxicillin  | X   | X          | X           | X          | X            | X          | X         | X          | X           | X        | X         |           |           |            |          |            |             |             |          |           |          |           |   |
|  | Ampicillin   | X   | X          | X           | X          | X            | X          | X         | X          | X           | X        | X         |           |           |            |          |            |             |             |          |           |          |           |   |
|  | Cloxacillin  | X   | X          | X           | X          | X            |            |           |            |             |          |           |           | X         |            |          |            |             |             |          |           |          |           |   |
|  | Penicillin   | X   | X          | X           | X          | X            |            |           |            | X           |          |           |           | X         |            |          |            |             |             |          |           |          |           |   |
|  | Piperacillin | X   | X          | X           | X          | X            |            |           |            |             |          |           |           |           |            |          |            |             |             |          |           |          |           |   |
| 1 <sup>st</sup> Generation Cephalosporin | Cefadroxil   | X   | X          |             |            |              | X          | X         | X          | X           | X        |           |           |           |            |          |            |             |             |          |           |          |           |   |
|  | Cefazolin    | Cefazolin shares no side chain and is safe to use in patients with a penicillin allergy history |            |             |            |              |            |           |            |             |          |           |           |           |            |          |            |             |             |          |           |          |           |   |
|  | Cephalexin   | X   | X          |             |            |              | X          |           | X          | X           | X        |           |           |           |            |          |            |             |             |          |           |          |           |   |
|  | Cephalothin  |   |            |             | X          |              |            |           | X          | X           |          |           |           | X         |            |          | X          |             |             |          |           |          |           |   |
| 2 <sup>nd</sup> Generation Cephalosporin | Cefaclor     | X   | X          |             |            |              | X          | X         | X          | X           | X        |           |           |           |            |          |            |             |             |          |           |          |           |   |
|  | Cefprozil    | X   | X          |             |            |              | X          | X         | X          | X           | X        |           |           |           |            |          |            |             |             |          |           |          |           |   |
|  | Cefotetan    |   |            |             |            |              |            |           |            |             |          | X         |           |           |            |          |            |             |             |          |           |          |           |   |
|  | Cefoxitin    |   |            |             | X          |              |            |           | X          |             |          |           | X         | X         |            |          |            |             |             |          |           |          |           |   |
|  | Cefuroxime   |   |            |             |            |              |            |           |            |             |          |           | X         | X         |            |          |            |             |             |          |           |          |           |   |
| 3 <sup>rd</sup> Generation Cephalosporin | Cefixime     |   |            |             |            |              |            |           |            |             |          |           |           |           | X          |          |            |             |             |          |           |          |           |   |
|  | Cefotaxime   |   |            |             |            |              |            | X         |            |             |          |           |           |           |            | X        |            | X           |             |          |           |          |           |   |
|  | Ceftazidime  |   |            |             |            |              |            |           |            |             |          |           |           |           |            |          | X          |             | X           |          |           |          |           |   |
|  | Ceftriaxone  |   |            |             |            |              |            |           |            |             |          |           |           |           |            |          | X          |             | X           |          |           |          |           |   |
| 4 <sup>th</sup> Generation Cephalosporin | Cefepime     |   |            |             |            |              |            |           |            |             |          |           |           |           |            | X        |            | X           |             |          |           |          |           |   |
| Carbapenems                              | Ertapenem    |   |            |             |            |              |            |           |            |             |          |           |           |           |            |          |            |             |             |          | X         | X        | X         | X |
|  | Imipenem     |   |            |             |            |              |            |           |            |             |          |           |           |           |            |          |            |             |             |          | X         | X        | X         | X |
|  | Meropenem    |   |            |             |            |              |            |           |            |             |          |           |           |           |            |          |            |             |             |          | X         | X        | X         | X |

X – Indicate antibiotics that have a similar side chain or structure and a higher risk for cross-sensitivity

## Penicillin Allergy Assessment and Testing:

In a large study evaluating the incidence of penicillin hypersensitivity (IgE mediated), it was found that in patients with a valid history of penicillin allergy, 21% had a positive skin test, while in patients with a questionable or invalid history, 10% and 4% had a positive skin test, respectively (10). Skin testing with both penicilloyl-poly-lysine (major determinant) and penicillin G (minor determinant) can identify up to 95% of patients with positive reactions. In the case of a negative skin test, 98% of patients will tolerate penicillin without any serious reaction (11). Penicillin skin testing or a graded challenge should be considered based on the patient's allergy history.

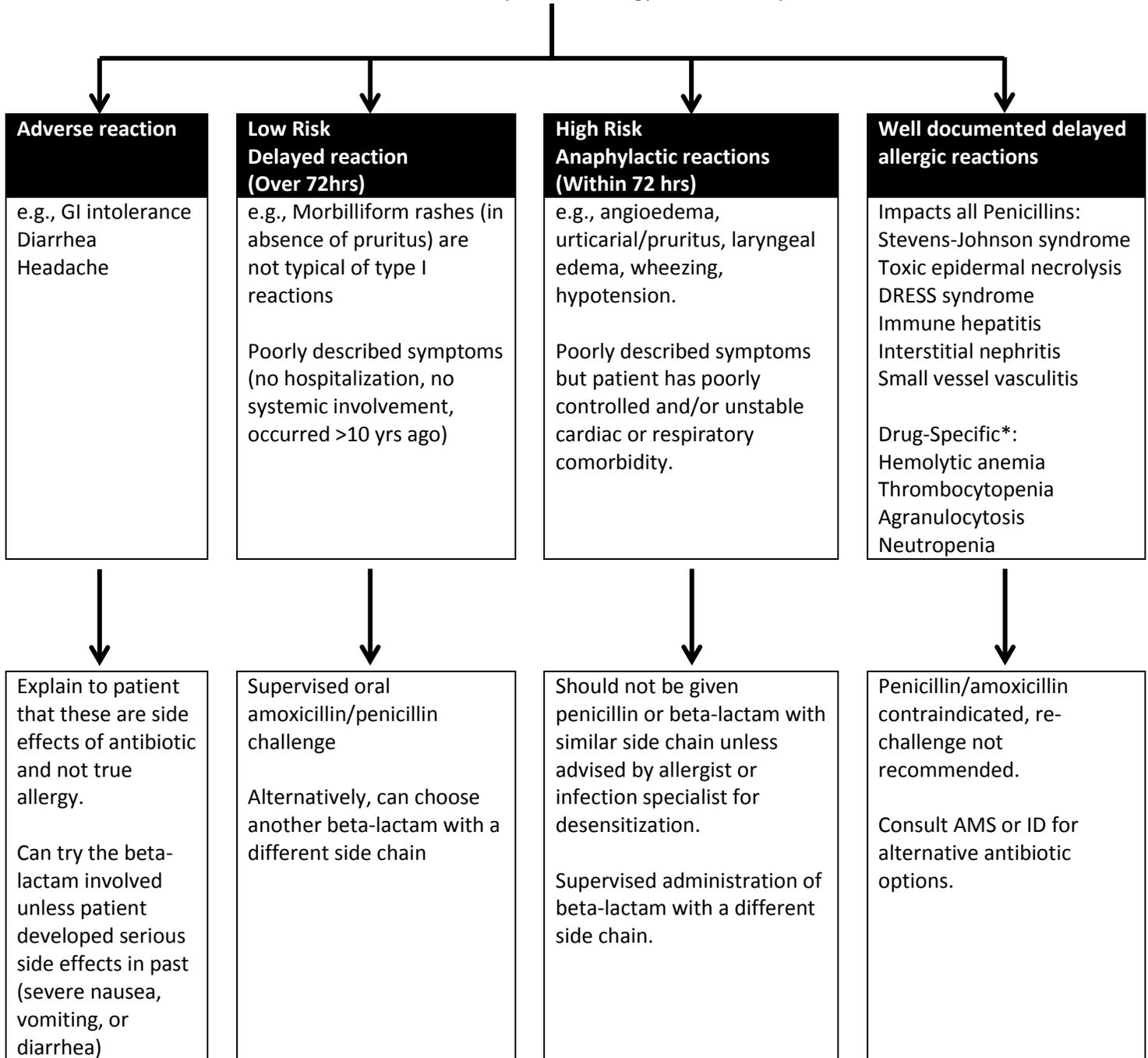
Despite the limitations of the available literature, the reported rate of allergic reaction with cephalosporins in a patient with a history of penicillin allergy is less than 1% (2). Furthermore, the rate of reaction to cephalosporin in patients with a positive penicillin skin test is approximately 2% (2). Therefore in patients with a history of non-severe penicillin reaction, the administration of a cephalosporin (that does not share a similar side chain as the culprit penicillin) can be safely given.

**Penicillin Allergy Questionnaire**

| <b>Rationale for Questionnaire</b>  |   |
|---|---|
| <ul style="list-style-type: none"> <li>Physicians are more likely to prescribe antimicrobials from other classes</li> <li>Patients with a beta-lactam allergy may be exposed to non-first line antibiotics</li> <li>Non-first line antibiotics may be less effective and more toxic increasing risk of undesirable outcomes (increased length of stay and <i>C. difficile</i> infections)</li> <li>Up to 90% of patients with a reported penicillin allergy can tolerate penicillin when challenged</li> <li>Questionnaire helps to identify patients that are deemed safe to undergo a penicillin challenge</li> </ul> |   |
| <b>Penicillin Allergy Questionnaire</b>   |   |
| <b>Skin Test</b>  |   |
| 1) Have you ever had a penicillin allergy skin test? <input type="checkbox"/> Yes <input type="checkbox"/> No   |   |
| <b>Allergy Questions</b>  |   |
| 1) Can you describe the reaction? _____   |   |
| 2) Was the reaction serious? <input type="checkbox"/> Yes <input type="checkbox"/> No   |   |
| 3) Can you remember the allergic reaction yourself? <input type="checkbox"/> Yes <input type="checkbox"/> No  |   |
| a. If not, who informed you of it? _____  |   |
| 4) How old were you at the time of reaction? _____  |   |
| 5) How long after starting the antibiotic did the reaction begin? _____   |   |
| 6) How was the reaction managed?  |   |
| a. Were you hospitalized? <input type="checkbox"/> Yes <input type="checkbox"/> No  |   |
| b. Was the medication discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No  |   |
| c. What happened after stopping the medication? _____   |   |
| 7) Which antibiotic was prescribed to you? _____  |   |
| a. Do you remember why it was prescribed? _____   |   |
| 8) Have you taken the antibiotic since? <input type="checkbox"/> Yes <input type="checkbox"/> No  |   |
| a. If yes, what was the outcome? _____  |   |
| 9) Have you experienced this same reaction without taking the antibiotic? <input type="checkbox"/> Yes <input type="checkbox"/> No  |   |
| <b>Assessment</b>   |   |
| <input type="checkbox"/> Adverse Reaction   | <ul style="list-style-type: none"> <li>GI intolerance, diarrhea, headache</li> </ul>  |
| <input type="checkbox"/> Low Risk Delayed Reaction (“Benign” rash)  | <ul style="list-style-type: none"> <li>“Benign” rash only (e.g. Morbilliform rashes in the absence of pruritus)</li> <li>Poorly described symptoms (no hospitalization, no systemic involvement, occurred &gt;10 years ago)</li> </ul>  |
| <input type="checkbox"/> High Risk Anaphylactic Reaction  | <ul style="list-style-type: none"> <li>e.g. Angioedema, urticaria/pruritus, laryngeal edema, bronchospasm, wheezing and hypotension</li> </ul>  |
| <input type="checkbox"/> Well Documented Delayed Reaction   | <ul style="list-style-type: none"> <li>Steven Johnson syndrome, toxic epidermal necrolysis, DRESS (drug reaction with eosinophilia and systemic symptoms), immune hepatitis, hemolytic anemia, thrombocytopenia, agranulocytosis, neutropenia, interstitial nephritis, small vessel vasculitis</li> </ul> |

**Algorithm for Management of Penicillin Allergy**

Risk stratification based on penicillin allergy assessment questionnaire



\*Drug-induced hemolytic anemia, thrombocytopenia, agranulocytosis, and neutropenia are **drug-specific**. Cross-reactivity between cephalosporins and penicillins does not appear to occur. Avoid the offending drug.

**Procedure for Amoxicillin/Penicillin Challenge**

- 1) Obtain consent from patient for oral challenge.
- 2) Give 1/10<sup>th</sup> dose of the intended antibiotic or a single dose oral challenge of amoxicillin 500mg x 1 (supervised by RN).
- 3) Observe patients for at least 60 minutes for any immediate hypersensitivity reaction. Check vital signs at baseline and every 30 minutes x 2 after the first dose.

**If patient develops anaphylaxis (see definition below):**

- **Give EPINEPHrine 0.3mg IM x 1. May repeat in 5 minutes**
  - **Give diphenhydrAMINE 50mg IV/PO x 1**
  - **Notify MRP immediately.**
- 4) Follow up oral challenge and document outcome of oral challenge in chart. If no reaction observed, proceed with full treatment dose.
  - 5) If no reaction observed, document in EMR (under allergies) that patient tolerated oral challenge of antibiotic.
  - 6) If no reaction observed and allergy is documented on Pharmanet profile, de-label the allergy using the “Request to Inactivate Adverse Reaction/Clinical Condition” form.
  - 7) Monitor patient throughout stay for any delayed hypersensitivity.

Anaphylaxis is likely when any **one** of the following criteria is fulfilled:

- 1) Acute onset of an illness involving skin, mucosal tissue, or both (generalized hives, pruritis or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:**
  - a. Respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
  - b. Reduced BP or associated symptoms (hypotonia, collapse, syncope, incontinence)
- 2) TWO OR MORE OF THE FOLLOWING that occur rapidly *after exposure to a likely allergen for that patient* (minutes to several hours)**
  - a. Involvement of the skin mucosal tissue (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)
  - b. Respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
  - c. Reduced BP or associated symptoms (hypotonia, collapse, syncope, incontinence)
  - d. Persistent gastrointestinal symptoms (crampy abdominal pain, vomiting)
- 3) Reduced BP *after exposure to a KNOWN allergen for that patient* (minutes to several hours)**
  - a. Systolic BP <90mmHg or >30% decrease from baseline